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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/618,178	07/18/2000	Stephen E. Lincoln	13151-2	9015

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/618,178	LINCOLN ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-82,85-87,91-98,100,102 and 106-115* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-82,85-87,91-98,100,102 and 106-115* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/14/05; 9/9/05; 9/6/05, 8/22/05, 7/12/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status

1. Claims 75-82, 85-87, 91-98, 100, 102 and 106-115 are pending.

Claims 75-82, 85-87, 91-98, 100, 102 and 106-115 are rejected.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Claim Rejections - 35 USC § 112 – second paragraph

2. Claim 94 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The new amendment, which results in claim 94 stating "wherein step (A) includes the step of assaying for the given allele using genetic bit analysis, allele specific hybridization, or allele specific amplification, including such amplification by a polymerase chain reaction or a ligase chain reaction" is vague and indefinite. The claim is indefinite because it is unclear to what "such amplification" is referring, since both genetic bit analysis and allele specific amplification require extension by a polymerase. Essentially, it is unclear what is added by the final phrase "such amplification" since the phrase lacks clear antecedent basis. Correction is required.

Priority

3. Applicant's claim of priority back to application 08/173,173, 07/775,786 and 07/664,837 is noted. The examiner was unable to determine whether these applications provide support for the entirety of the current claims and therefore the

claims are given the effective date of the immediate parent 09/088,820, which provides express support (except for claim 50, as detailed below).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 75-82, 85, 86, 91-93, 95, 96-98, 102, 106-109 and112-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton et al (PCR Meth. Appl. (August 1993) 3:13-22) in view of Ledwina et al (Biometrics (1980) 36:161-165) and further as motivated in view of JeanPierre (Ann. Hum. Genet. (1992) 56:325-330).

Kimpton teaches a method of claims 75 and 96 of determining the genotype at a locus within genetic material obtained by PCR amplification from a subject (page 14) comprising:

a) Reacting the material at the locus to produce a first reaction value (see page 14, columns 1-3, subheading "Locus specific amplification conditions"),

b) forming a data set including the first reaction value by assembling reaction value data points for the samples, each reaction-value data point corresponding to a respective one of the samples and including at least one reaction value (here the data points represented by each of the separate peaks in figure 1 represents a different sample and are assembled in figure 2) (see pages 14-16),

e) determining the genotype and confidence score for each reaction value data point, thus determining the genotype and confidence score at the genetic locus for each sample (here, table 2 on page 17 provides for each reaction point the genotype and a standard deviation based on the data obtained from step d) (page 16 and page 17).

With regard to claim 77 and 78, Kimpton expressly teaches reacting the material at multiple loci (page 14, table 1).

With regard to claims 80-82, 114, 115, on page 17, Kimpton expressly considers multiple alleles in the probability distributions, particularly in table 2 which expressly notes that the method is applicable to any number of alleles.

With regard to claim 85, 97, 98, 108, 109, Kimpton teaches confidence score determination (see pages 16 and 17).

With regard to claim 86, 102, 107, Kimpton expressly selected the loci for their discrimination ability and teaches that several different loci may be analyzed (page 16, column 1).

With regard to claims 91-93, Kimpton expressly teaches the use of multiple data points derived from multiple runs of the automated apparatus including multiple data sets in the exemplified method and apparatus (page 16, especially figure 2).

With regard to claim 95, Kimpton expressly teaches that the locus may be dinucleotide or tetranucleotide repeats (page 13).

With regard to claim 112, Kimpton teaches obtaining data that correlates the reaction value to the genotype (see pages 16 and 17).

With regard to claim 113, Kimpton demonstrates optical signals (see figure 1, where dye labeled DNA products are detected).

While Kimpton uses the Hardy-Weinberg test, Kimpton does not establish a distribution set of probability distributions and Kimpton does not then apply the reaction value of the distributions to detemine a measure of a conditional probability of each genotype of interest at the locus.

Ledwina teaches a method in which genotypes can be determined in which the Hardy Weinberg test is modified such that the steps of:

c) establishing a distribution set of probability distributions and associating hypothetical values with corresponding probabilities for each genotype of interest (see page 162 and page 163),

d) applying the first value to each pertinent probability distribution to determine a measure of conditional probability of each genotype of interest (see page 162 and page 163, especially "conditional distribution of T given Z=z" equation on page 163).

With regard to claim 76 and 79, Ledwina teaches a plurality of distributions which are hypothetical (see page 162, "common probability distribution of (T,Z) is multinomial with 1/2m(m+1) cells and with the vector of cell probabilities g=(g...).".

Further, JeanPierre motivates the use of computation of unknown genotypes to analyze the conditional probabilities relative to a distribution of hypothetical reaction values (see page 330).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Kimpton to use the conditional probability distribution method of Ledwina since Kimpton notes that the anlaysis uses the Hardy-Weinberg equilibria (see abstract) and since Ledwina states "The class of admissible tests for Hardy-Weinberg equilibrium in a multi allelic system is characterized. The standard goodness of fit chi square test is shown to be admissible for systems of two or more alleles. The conditional probability distribution required to determine the exact significance level of this test is presented (see abstract)". An ordinary practitioner would have been motivated to apply this hypothetical distribution analysis to genotyping since Jeanpierre notes the gains from creating such a distribution include avoiding hazards such as incorrectly using the simple average of the conditional probabilities instead of the harmonic mean, to more accurately determine the genotype (see page 330).

7. Claims 75-82, 85-87, 91-98, 100, 102, 106-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kimpton et al (PCR Meth. Appl. (August 1993) 3:13-

22) in view of Ledwina et al (Biometrics (1980) 36:161-165) and further as motivated in view of JeanPierre (Ann. Hum. Genet. (1992) 56:325-330) and further in view of Goulet et al.

Kimpton in view of Ledwina as motivated by JeanPierre teach the limitations of claims 75-82, 85, 86, 91-93, 95, 96-98, 102, 106-109 and 112-115 as discussed above. Kimpton in view of Ledwina as motivated by JeanPierre does not teach genetic bit analysis, which includes allele specific amplification, nor the particular alleles listed.

Goelet teaches genetic bit analysis methods, including allele specific amplification methods (see entire document, expecially pages 10-13). Goulet teaches single specific nucleotide alleles (see page 40, example 3). Goulet also shows a mutation which is associated, at least indirectly, with a restriction site (see figure 2).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Kimpton in view of Clark with the use of genetic bit analysis or allele specific amplification to develop the data since Goelet states "The current invention provides a method that can be used to diagnose or characterize nucleic acids in biological samples without recourse to gel electrophoretic size separation of the nucleic acid species. This feature renders this process easily adaptable to automation and thus will permit the analysis of large numbers of samples at relatively low cost (page 8, lines 27-33)". An ordinary practitioner would have been motivated to substitute the equivalent genetic bit analysis method for PCR in order to minimize the need for gel electrophoresis and enhance the automatability of the process as expressly motivated by Goulet in order to speed analysis and minimize costs.

Response to Arguments

8. Applicant's arguments filed August 22, 2005 have been fully considered but they are not persuasive.

Applicant argues that Kimpton teaches away from the use of probability determinations because Kimpton preferred an "unambiguous" allele identification method. In fact, Kimpton relied upon mathmatical analysis of the bands in order to determine the sample gene diversity as shown on page 15, under the subheading "statistical calculations". Kimpton clearly relied upon such methods to determine the allele frequency. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Kimpton had a preferred method for analysis of the alleles, this embodiment does not constitute a teaching away from such embodiments such as those suggested by the Ledwina reference.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does

not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant then provides a mathematical argument in which the specific formula of Ledwina is argued as not relevant to complete genotype enumeration. However, no such element is found in the claims. The claims simply require ONE distribution with ONE hypothetical value relating to ONE genotype. Thus, Ledwina need not teach conditional probabilities for complete genotype enumeration because this is not a feature of the claims. Further, Ledwina expressly teaches the use of conditional probability analyses when associated with genotyping. An ordinary practitioner, faced with data generated by the method of Kimpton and the suggestion to use the Hardy-Weinberg equation of Kimpton, would have been motivated for the reasons given in the rejection to use the conditional probability methods of Ledwina.

9. In response to applicant's argument that Ledwina, Kimpton and JeanPierre are nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, all three references are concerned with genotyping of humans and with the statistical analyses necessary for proper genotyping. These are nearly identical problems and each reference is pertinent to the same issues and problems.

The arguments relating to Goulet appear to rely upon overcoming the prior rejections. Since these rejections are maintained, so is the 103 over Goelet.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637

10/1/05